REMARKS

Reconsideration is respectfully requested. Claims 1-59 have been canceled. Claim 60 has been amended. Claims 60-69 are pending and under consideration.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Amendment

Claim 60 has been amended for clarity.

Claim Rejection Under 35 U.S.C. § 103

Claims 60-69 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kayyem et al. (WO 98/20162) ("*Kayyem*"), in view of Shuber (US 5,633,134) ("*Shuber*").

To establish a *prima facie* case the prior art reference(s) must teach or suggest each and every limitation of the rejected claims. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. §2142.

Kayyem And _Shuber_, In Combination, Do Not Expressly Disclose Each And Every Limitation Of The Claimed Methods.

1. Neither _Kayyem nor Shuber_ teaches first and second labeled probes that are both substantially complementary to the same domain.

Claim 61-69 depends on claim 60, which requires "a first label probe" and " a second label probe," both of which are "substantially complementary to said first domain." *Kayyem* expressly discloses a composition comprising an anchor sequence and a probe that hybridize to two different domains, not the same domain as required by claim 60. Specifically *Kayyem* states:

> [C]ompositions are provided comprising ... a first single stranded anchor sequence. A second single stranded nucleic acid is provided, which contains a probe region and a region substantially complementary to the

> anchor sequence.... A target sequence which is substantially complementary to the probe region is then added[.]
>
> *Kayyem* page 36, lines 1-6.

Thus *Kayyem* discloses a probe that hybridizes to two domains on two different sequences - one is on the anchor sequence and the other is on the target sequence, instead of the same domain of the target sequence, as required by claim 60.

Kayyem also expressly discloses two probes that hybridize to two different domains, not the same domain as required by claim 60. Specifically, *Kayyem* states:

> Upon binding of the target sequence, which contains a first target domain for the first probe sequence and second target domain for the second probe sequence, ... transfer may occur.
>
> *Kayyem*, page 36, lines 12-14.

Thus, the first and second probes disclosed by *Kayyem* hybridize to two different domains of the target sequence instead of the same domain of the target sequence, as required by claim 60. As such, *Kayyem* does not expressly teach two probes that are both substantially complementary to the same domain. This defect is not cured by *Shuber*.

Shuber discloses the testing for the presence or absence of multiple mutations in one gene or multiple genes using allele specific oligonucleotide (ASO) probes. See Abstract. Specifically, *Shuber* discloses the hybridization of multiple probes simultaneously by using pooled ASO probes. See col. 5, lines 38-39. However, the probes as disclosed by *Shuber* are complementary to different genes/sequences, or different mutation sites of the same genes/sequences. See col. 5, Table 1. These probes are not complementary to the same domain of the target gene as claim 60 requires.

Shuber also discloses that "normal (i.e. wild-type) oligonucleotides or portions thereof" can be added together with detection probe. See col. 3, lines 64-65, and col. 8, lines 21-36. However, *Shuber* also instructs that such wild-type oligonucleotides should be "cold (i.e. non-labeled)" and added "to the hybridization reaction preferably in a concentration in the range of about 1-100 times the concentration of labeled ASO." See col. 3, line 67 to col. 4, line 2. Therefore, such wild-type oligonucleotides as disclosed by *Shuber* lack the "label probe"

requirement of claim 60. In fact, *Shuber* explains that the purpose of adding the wild-type oligonucloetides is not to use them as probes; rather:

> [U]nlabelled normal oligonucleotides or nucleotide portions outcompete the mutation specific labelled ASOs, where normal sequence is present thereby reducing the degree of non-specific hybridization occurring between the mutation specific ASOs and the normal wild-type sequence.
>
> Col. 4, lines 2-8.

As such *Shuber* does not teach multiple probes with labels for determining nucleotides at the detection position as the Examiner alleges.

2. Neither *Kayyem nor Shuber* teaches teach first and second probes having different nucleotides at the same interrogation position.

Claim 60 recites "a first label probe...comprising a first nucleotide at an interrogation position and...a second label probe...comprising a second nucleotide at said interrogation position." Both the first probe and the second probe are "substantially complementary to said first domain," and have different nucleotides at the "interrogation position."

Claims 60 not only requires that two probes compete for hybridization to the same domain, as discussed above, but also requires that the two probes have different nucleotides at the same interrogation position. Both *Kayyem* and *Shuber*, however, expressly disclose that the probes hybridize to different domains. As discussed above, *Kayyem* discloses a probe that hybridizes to two domains on two different sequences - one is on the anchor sequence and the other is on the target sequence, and two probes that hybridize to two different domains of the target sequence. *Shuber* then discloses multiple probes that are complementary to different genes/sequences, or different mutation sites of the same genes/sequences. Therefore, neither *Kayyem* nor *Shuber* discloses two or more probes that are complementary to the same domain of the target same, and neither discloses probes having different nucleotides at the "interrogation position" as claim 60 requires. As such, *Kayyem* and *Shuber* fail to disclose this limitation of claim 60.

Therefore, *Kayyem* and *Shuber* taken together do not teach all of the elements of independent claim 60, and of claims 61-69 dependent thereon. As such, claims 60-69 are not obvious over *Kayyem* in view of *Shuber*. Applicants respectfully request the rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

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Jeffery P. Bernhardt, Reg. No. 54,997 for
Robin M. Silva, Reg. No. 38,304

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Customer No.: 32940
555 California Street, Suite 1000
San Francisco, CA 94104-1513
Telephone: (415) 781-1989
Facsimile: (415) 398-3249

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